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REVIEW

Clinical Development of AKT Inhibitors and Associated Predictive Biomarkers to Guide Patient Treatment in Cancer Medicine

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Abstract: The serine/threonine kinase AKT is a critical effector of the phosphoinositide 3-kinase (PI3K) signaling cascade and has a pivotal role in cell growth, proliferation, survival, and metabolism. AKT is one of the most commonly activated pathways in human cancer and dysregulation of AKT-dependent pathways is associated with the development and maintenance of a range of solid tumors. There are multiple small-molecule inhibitors targeting different components of the PI3K/AKT pathway currently at various stages of clinical development, in addition to new combination strategies aiming to boost the therapeutic efficacy of these drugs. Correlative and translational studies have been undertaken in the context of clinical trials investigating AKT inhibitors, however the identification of predictive biomarkers of response and resistance to AKT inhibition remains an unmet need. In this review, we discuss the biological function and activation of AKT, discuss its contribution to tumor development and progression, and review the efficacy and toxicity data from clinical trials, including both AKT inhibitor monotherapy and combination strategies with other agents. We also discuss the promise and challenges associated with the development of AKT inhibitors and associated predictive biomarkers of response and resistance.

Keywords: AKT, PI3K, m-TOR, AKT inhibitor

Introduction

The PI3K–AKT–mTOR signaling pathway is one of the most frequently dysregulated pathways in human cancer.[1] AKT is a key effector of this signaling cascade, which controls a number of key cellular processes, such as metabolism, motility, growth, and proliferation, and supports the survival, expansion and dissemination of cancer cells.[2] Dysregulation of AKT-dependent pathways is associated with the development and maintenance of numerous solid tumors,[3–5] and as a result, AKT has been relentlessly pursued as a therapeutic target in modern cancer drug development for more than a decade. A number of small-molecule inhibitors targeting various nodes in the PI3K–AKT–mTOR pathway have been investigated in solid tumors and are at various stages of clinical development.

Broadly, there are two major classes of small-molecule AKT inhibitors being investigated in the clinic: allosteric and ATP-competitive inhibitors.[6] Allosteric inhibitors (such as miransertib (ARQ 092) and MK-2206)[6] interfere with PH-domain mediated membrane recruitment (the first step in AKT activation) and inhibit AKT kinase activation and AKT phosphorylation. In contrast, ATP-competitive inhibitors of AKT (such as ipatasertib and capivasertib) bind to the active kinase, in which the PH-

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domain has shifted from the kinase domain and exposed the ATP-binding pocket site, thus inhibiting ATP binding. Targeting AKT with small-molecule inhibitors may enhance approved or investigational anticancer treatments, and several allosteric and ATP-competitive AKT inhibitors have now been tested in clinical trials.

Clinically, the development of AKT inhibitors in solid tumors has been complex, however there have been recent successes in select populations using combination strategies, such as capivasertib in combination with fulvestrant in AKT1 E17K mutant hormone receptor positive metastatic breast cancer.[7] AKT is a significant downstream effector of PI3K signaling; interestingly, there are three different PI3K inhibitors FDA-approved for the treatment of follicular lymphoma, namely idelalisib, copanlisib, and duvelisib, and while these drugs vary in regard to the isoforms that they target, small-molecule inhibitors of AKT have not yet been explored in this context.

In this review, we discuss the biological function of AKT, discuss its contribution to tumor development and progression, and review up-to-date efficacy of clinically relevant AKT inhibitors in solid tumors, as monotherapy and in combination with other agents. We discuss the issues and limitations involved with targeting the AKT–PI3K–mTOR pathway, associated predictive biomarkers and predict future challenges for these novel anticancer agents.

Biology: AKT Structure and Function

AKT comprises a family of serine/threonine kinases, consisting of three isoforms (AKT1, AKT2 and AKT3), regulated upstream by the activation of PI3K, following growth factor stimulation. Several downstream substrates of activated AKT play a major role in the regulation of cell size, cell cycle progression, glucose metabolism, genome stability, transcription, protein synthesis and inhibition of pro-apoptotic proteins.[8–10] The three AKT isoforms are encoded by different genes with high sequence homology and display a conserved protein structure (Figure 1).[11] All three AKT proteins have three functional domains: a N-terminal fragment with a pleckstrin-homology (PH) domain, a central kinase domain (KD) and a C-terminal fragment with a regulatory region (RR) containing a hydrophobic motif (Figure 1). Enhanced activation of all the isoforms can be implicated in tumor development and progression, though interestingly their functional spectrum shows some variety: AKT1 has a suggested role in cell proliferation and survival, while AKT2 exercises its control over metabolism, regulates cytoskeleton dynamics;

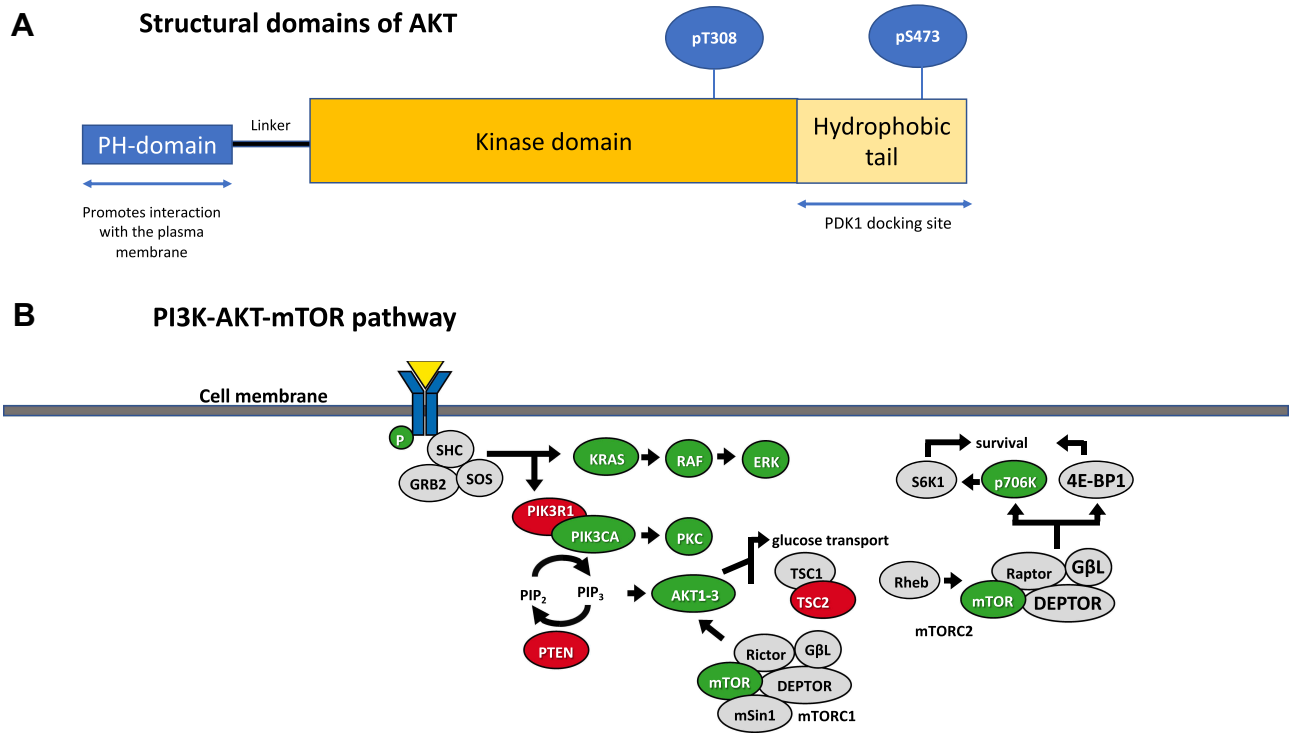


Figure 1 (**A**) Structural domains of AKT. AKT1, AKT2 and AKT3 share common domain structure with other members of the cAMP-dependent, cGMP-dependent and protein kinase C (AGC) subfamily of protein kinases: this consists of an N-terminus pleckstrin homology (PH) domain, a large central kinase domain and a C-terminus hydrophobic domain. (**B**) The PI3K-AKT-mTOR pathway. A selection of the downstream targets of AKT is shown.

AKT3 has a more restricted expression pattern, with increased expression in brain tissue, and is implicated in mediating cell growth processes along with AKT1.[12]

AKT Activation

Initiating signaling through the PI3K/Akt/mTOR pathway occurs through a number of different mechanisms, and typically begins from the plasma membrane, initiated by receptor tyrosine kinases, G-protein coupled receptors and immune receptors.[13] These receptors are usually activated by ligand binding, which lead to signals that classically activate class I PI3K, leading to the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3) from phosphatidylinositol-4,5-bisphosphate (PI45P2). PIP3 and PI34P2 then bind to the PH domain of AKT which leads to the re-localization of AKT to the plasma membrane, which triggers membrane recruitment and potentiates signals that ultimately lead to the activation of AKT. Phosphatidylinositol-3,4-bisphosphate (PI34P2) can also be produced by either dephosphorylation of PIP3 by 5-phosphatases or by activation of class II PI3Ks that phosphorylate phosphatidylinositol-4-phosphate (PI4P).[13]

Once at the membrane, AKT undergoes further conformational changes, resulting in the phosphorylation of Thr308 residue by phosphoinositide-dependent kinase-1 (PDK1) and phosphorylation of Ser473 by target of rapamycin complex 2 (mTORC2) of the mammalian target of rapamycin (mTOR) kinase (Figure 1).[14] In addition to mTORC2, multiple different kinases, including DNA-PK (DNA-dependent protein kinase) which is a PI3K-like kinase (PIKK), have been shown under certain conditions to phosphorylate AKT on Ser473.[15] Through phosphorylation, activated AKT exerts control over a vast number (>100) of protein substrates distributed throughout the cell including the plasma membrane, various endomembrane compartments, the mitochondria, cytosol, and the nucleus.[13]

mTOR, is a key downstream node in PI3K/AKT signaling, and a key cell metabolism regulator; activated mTOR phosphorylates ribosomal protein S6 kinase (p70S6K) and eIF4E binding-protein-1 (4E-BP1) to promote protein synthesis. Tuberous sclerosis complex 1 and 2 (TSC1 and TSC2) tumor suppressors, which are negative regulators of mTOR/S6K pathway, are phosphorylated by AKT, resulting in their inhibition.[16,17] AKT phosphorylates the proline-rich AKT substrate of 40 kDa (PRAS40) at Thr246 and the yes-associated protein (YAP) at Ser127 to induce their interaction with 14–3-3, which correlates with their inactivation.[18–20] Further negative regulators of the PI3K/AKT signaling pathway, include tumor suppressor genes and phosphatases PTEN (phosphatase and tensin homolog), PP2A (protein phosphatase 2A) and PHLPP (PH domain and leucine rich repeat protein phosphatase), which dephosphorylate PIP3, AKT pThr308 and AKT pSer473 respectively. PIP3 functions as a second messenger in the PI3K pathway that binds and activates proteins that have a pleckstrin homology domain, such as AKT1, and triggers their activation and localization to the plasma membrane, promoting cellular proliferation and survival.[21] Consequently, loss of PTEN, a frequent aberration in human cancer (frequency of PTEN loss by IHC 30%, PTEN mutations 6%)[22] leads to PI3K/AKT pathway activation.

AKT also exerts its effect on cell cycle progression by phosphorylating and inhibiting cyclin dependent kinase (CDK) inhibitors, p21 and p27, which function as G1 checkpoints to arrest the cell cycle.[17] AKT regulates apoptosis through inhibition of BAD, BCL-2-like protein 11 (BIM), caspase 9, and forkhead box protein O1 (FoxO1).[23–25] It also phosphorylates MDM2, allowing its entry into the nucleus, which results in p53 degradation.[26,27] In reality, there are numerous AKT substrates, which have been reported in the literature and been extensively validated, involving multiple cellular processes functions, including cell growth, proliferation and survival, cellular metabolism, glucose uptake and angiogenesis.[13]

Deregulation of AKT Pathway and Role in Oncogenesis

AKT signaling plays a key role in multiple pathways involved in tumorigenesis, and hyperactivation of the pathway is a common event in cancer. There is significant overlap and crosstalk between substrates and substrate functions of AKT, and AKT regulates many of its cellular functions through phosphorylation.[13] Although the status of all the activators, modulators and downstream effectors of AKT play a critical role in tumor development, aberrant AKT activation itself is highly oncogenic.

Aberrant activation of AKT in cancer can occur through a number of mechanisms, due to amplification and/or mutation of AKT, or via genomic changes at various levels in the pathway. PI3K/AKT pathway aberrations have been identified in up to 40% of all tumor types: PTEN loss by immunohistochemistry occurs most frequently (30%), followed by mutations in PIK3CA (13%), PTEN (6%) and AKT (1%).[22] AKT1 is the most frequently mutated isoform in solid tumors, though its frequency varies by cancer type: the overall frequency of

AKT1 hotspot mutations is low (<1%) in cancer, but the overall frequency of PI3K pathway activation is high. For example, in breast cancer, mutations of the PI3K catalytic alpha subunit (PIK3CA) are common events, occurring in 9–45% of breast cancer according to the subtype, PTEN loss of function occurs in 13–35% and AKT substitutions (2–4%) or amplification (5–10%) have also been described.[28] Frequency of pathway activation then differs again by cancer subtype, where up to 50% of HR+ breast cancer demonstrates PI3K/AKT pathway hyperactivation (predominantly via by *PIK3CA* point mutations in HR + tumors), 5–10% of ER+ metastatic breast cancer tumors harbor somatic PTEN mutations[29] and an estimated 7% of ER+ breast cancers, pathway activation can occur through mutation in *AKT1*, predominantly *AKT1*^{E17K} (~80%).[30] Combined activating mutations in PIK3CA and AKT1, with inactivating PTEN mutations occur in ~25%–30% of advanced triple negative breast cancer (TNBC).[31] The pathway is also deregulated in human epidermal growth factor receptor 2 (HER2)-enriched breast cancer where it is involved in the development of resistance toward anti-HER2 agents.[32] Given the frequency of dysregulation, AKT inhibitors are an important and promising class of antitumor agents for targeting breast cancer.

AKT2 amplifications occur more frequently than mutations: analysis of pan-cancer MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017) on (10,336 patients/10,945 samples) on the cBioPortal genomic database demonstrate that AKT2 amplification is found in up to 4% of endometrial cancer (0.5% frequency of mutation), 4% of ovarian (0.5% mutation frequency) and 3.6% of small cell lung cancer (Figure 2).[33,34] In the same cohort, AKT1 mutations are more common than amplification (Figure 2), with alterations in AKT occurring in 4.6% of endometrial and 5% of breast cancer, as well as approximately 1.5% of lung, bladder, ovarian and colorectal cancers. AKT3 alterations are also infrequent and analysis of the pan-cancer MSK-IMPACT Clinical

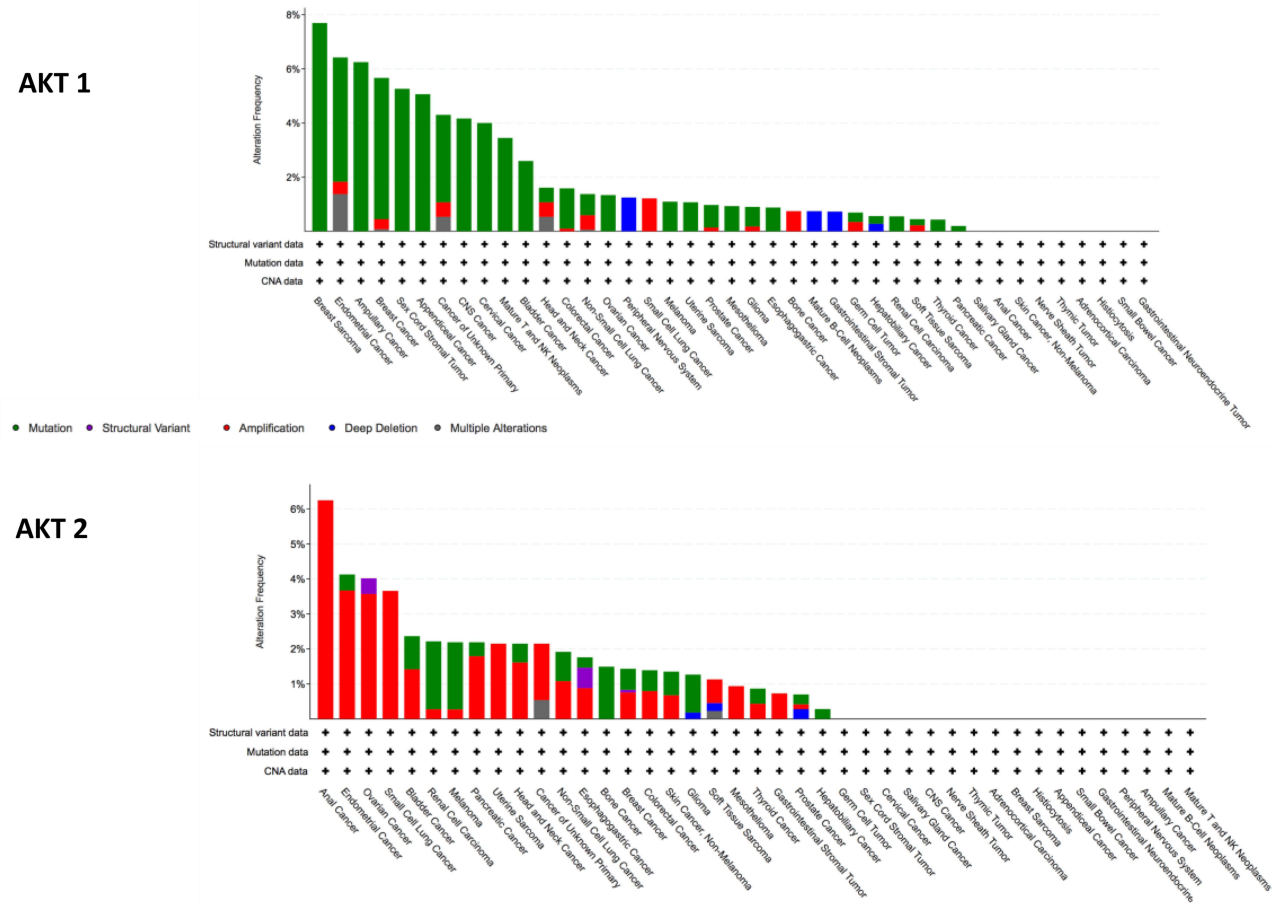


Figure 2 Frequency of AKT1 and AKT2 alterations from analysis of MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017), cBioPortal genomic database.[33,34]

Sequencing Cohort shows that AKT3 alterations are found rarely in breast cancer (0.45% frequency of mutation; 1.06% frequency of amplification), endometrial cancer (3.21% frequency of mutation; 1.83% frequency of amplification), and somewhat more frequently in melanoma (6.08% frequency of mutation) and tumors of the peripheral nervous system (1.25% frequency of amplification, 3.75% frequency of deep deletion) (Figure 2). In preclinical breast cancer models, AKT3 expression has been shown to be markedly upregulated to the AKT Inhibitor MK2206 in Breast Cancer MK2206-resistant cells, which may provide a rationale for developing therapeutics targeting AKT3 to overcome acquired resistance in breast cancer.

Overexpression or activating mutations upstream of AKT in the PI3K/AKT pathway can lead to AKT activation, as may loss of tumor suppressor proteins, such as PTEN, PHLPP, PP2A. Germline PTEN loss-of-function mutations can lead to dominant AKT activation as a driving oncogenic event, for example in Cowden syndrome, which leads to an increased risk of breast, thyroid and endometrial cancer.[35] Indeed, exceptional durable responses to AKT Inhibition have been demonstrated in patients with breast cancer and germline PTEN mutations.[35]

Potential Biomarkers of AKT Activity

In the era of precision medicine, identifying predictive biomarkers of response has become a key goal of translational cancer research. Accordingly, the aim is to establish biomarkers that predict "addiction" to the PI3K–AKT pathway to match patients with appropriate inhibitors. Multiple translational studies have been extensively undertaken in the context of clinical trials, however results are still inconclusive. For instance, investigating the phosphorylation levels of downstream effectors of AKT in order to determine whether AKT inhibition effectively downregulates PI3K hyperactivation has been pursued, albeit with mixed outcomes. In the STAKT trial, a two-stage, double-blind, randomized, placebo-controlled, "window-of-opportunity" study in patients with newly diagnosed ER+ invasive breast cancer, post-treatment phosphorylation of downstream AKT effects were significantly decreased from baseline versus placebo (n = 11) in pGSK3β, pPRAS40, pS6, while pAKT (and nuclear FOXO3a) also increased in accordance with the mechanism of capivasertib.[36] Another window-of-opportunity trial which investigated MK-2206 demonstrated only a modest effect on downstream effectors, such as pS6 and PTEN phosphorylation.[37] Comprehensive phosphoproteomic analysis was undertaken in patients with early HR-negative/ HER2-positive breast cancer and triple negative breast cancer (TNBC) of the I-SPY2 trial, which was a multicenter, Phase II randomized neoadjuvant platform trial that screened experimental therapies to identify potential predictive biomarker signatures.[38] In this study, in the HER2-positive subset, increased levels of pAKT, pSGK, pmTOR, and pTSC2 levels before neoadjuvant treatment with MK-2206 and standard therapy correlated positively with pathological complete responses.[38] In contrast, in the TNBC cohort, responding patients had lower levels of AKT pathway phospho-proteins, such as pAKT, pmTOR, and pTSC2 and pathway mutations did not appear to account for these associations.[38]

In the PAKT and LOTUS phase II trials discussed further below,[39,40] which combined either capivasertib or ipatasertib, respectively, with paclitaxel, combination treatment resulted in improved PFS in patients with TNBC, with the benefit more pronounced in the subgroup of patients with PIK3CA/AKT/PTEN alterations. Interestingly, the same benefit was not observed in LOTUS among PTEN-low patients.[39] In addition, in the molecularly selected Phase III trial investigating ipatasertib in combination with paclitaxel,[41] patients with PIK3CA/AKT1/PTEN-altered TNBC did not achieve improved PFS, results which differ from findings in both randomized phase II trials of AKT inhibitors in TNBC (LOTUS and PAKT). A unifying theme in these biomarker-driven breast cancer trials is a clear lack of correlation between PI3K/AKT pathway alterations and efficacy of AKT inhibitors.[42–44] There are clearly elements in this intricate pathway that the currently designed clinical trials are not taking into account. The complex network of the PI3K-AKT pathway, including crosstalk and negative feedback loops, is certainly a potential cause for the disappointing efficacy using AKT inhibitors, such as capivasertib in the PI3K/AKT/PTEN altered population.

An exception to these inconsistencies, appears to be the *AKT1* E17K mutation, which predicts for response to most ATP-competitive inhibitors, but not allosteric AKT inhibitors. Aside from this alteration, there do not appear to be other robust predictive biomarkers of AKT inhibitor response. Recent successes in targeting the *AKT1* E17K mutation in solid tumors only underscore the importance

of understanding the impact each PI3K/AKT pathway alteration has on binding to a specific molecularly targeted agent. Novel biomarkers are clearly urgently needed to increase the impact of AKT inhibitors as part of biomarker-driven clinical trials. These studies may incorporate other AKT mutations, AKT amplification, and other non-AKT biomarkers (such as PTEN loss) and will likely be critical in uncovering potential biomarkers of response and resistance. Given the complexity of the pathway, it is likely that multiple context-specific biomarkers to better predict response are needed.

The Clinical Development of AKT Inhibitors

Inhibiting PI3K/AKT signaling has long been an attractive therapeutic approach in oncology. Numerous compounds that inhibit the pathway at all levels are now in clinical development, in both monotherapy and combination strategies.[45] Notably, there are currently several ATP-competitive inhibitors of AKT at early stages of clinical development. All ATP-competitive inhibitors in clinical development are able to target all three AKT isoforms (ie, AKT1, AKT2 and AKT3), though with varying degrees of potency; allosteric inhibitors generally spare AKT3. Here, we describe progress to date, including most recent developments in strategies used to target AKT in solid tumors.

Monotherapy with AKT Inhibitors

Allosteric Inhibitors

Until recently, AKT inhibitors utilized as monotherapy agents, had failed to build on initial promise demonstrated in pre-clinical models. For instance, the following allosteric AKT inhibitors have been all been tested in phase I/II trials, including MK-2206, ARQ 092, ARQ 751 and BAY1125976, and while some of these agents have demonstrated manageable safety profiles,[46–49] limited clinical activity in phase II monotherapy trials has been observed.[50–54] Allosteric AKT inhibitor MK-2206 for example, is predominantly an AKT1/2 inhibitor with reduced potency against AKT3, shown to have single-agent activity against a range of cell lines harboring RTK activation, PTEN loss/mutation and/or AKT2 amplification.[55] MK2206 was previously the most clinically advanced allosteric inhibitor of AKT: a phase I trial of MK-2206 monotherapy in patients with solid tumors demonstrated a MTD of 60mg on alternate days with DLTs of skin rash and stomatitis; drug-related AEs included rash (51.5%), nausea (36.4%), pruritus (24.2%), hyperglycemia (21.2%), and diarrhea (21.2%).[56] While single-agent MK-2206 showed evidence of significant AKT pathway blockade (on-target PD tumor effects such as a decrease in AKT pSer473 were observed), its toxicity profile was challenging, although more intermittent dosing schedules seemed to be better tolerated.[49] Given the limited antitumor activity seen with MK-2206 monotherapy in phase II trials across a range of tumor types, attention then switched to combination trials. The allosteric inhibitor ARQ 092 has also been tested in both solid and hematological cancers, and demonstrated acceptable tolerability, though with limited activity and few partial responses clinically.[47,57] ARQ 751 is currently being tested in a Phase 1 study for solid tumors with PIK3CA/AKT/PTEN mutations (NCT02761694), both as monotherapy and in combination with other anti-cancer agents.

ATP-Competitive Inhibitors

Multiple ATP-competitive AKT inhibitors have also undergone clinical testing in phase I trials, including GSK2141795, GSK690693 and LY2780301.[58,59] The antitumor activity of these agents as monotherapy in molecularly unselected patient populations has been generally disappointing: GDC-0068 and AZD5363 have been tested in a number of monotherapy trials with limited activity; GDC-0068 has also demonstrated modest antitumor activity (30% stable disease) across tumor types in a phase I study.[60] Recently, capivasertib (AZD5363) a selective ATP-competitive pan-AKT kinase inhibitor has shown clinically meaningful activity in patients with various tumor histologies who have *AKT1* E17K mutations or PTEN mutations.[61,62]

The *AKT1* E17K mutation plays a crucial role in cancer development and is mutually exclusive to *PIK3CA* mutations and PTEN loss,[30,63,64] suggesting that the mutational activation of the phosphatidylinositol 3-kinase pathway by any one of these means may be biologically equivalent. Significant antitumor responses were initially reported using capivasertib in patients with heavily pretreated *AKT1* E17K mutant solid tumors in a basket trial (including 20 patients with ER-positive (ER+) metastatic breast cancer, where the objective response rate (ORR) was 20% and median progression-free survival (PFS) was 5.5 months.[65]

Recently, the results of a subprotocol of the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-Match) trial reported promising ORR with capivasertib in *AKT1* E17K-mutated tumors.[61] Among 35 treated patients, the objective response rate was 28.6%, the

median PFS was 5.5 months, with a median duration of response of 4.4 months among responders; one patient achieved complete response (CR).[61] Of those patients with confirmed PR, 7 had HR-positive/ERBB2-negative breast cancer, 1 had uterine leiomyosarcoma, and 1 had oncocytic parotid gland carcinoma.[61] The majority of patients treated had either breast cancer (51%) or gynecologic cancers (31%), and while responses were seen across different subgroups, it may be difficult to extrapolate these findings to non-breast and non-gynecology cancers due to the small numbers treated. In addition, the documented adverse event profile in this study was higher than that reported in similar studies of capivasertib, as there were 26% of patients with grade 3 or higher hyperglycemia, and 11% with grade 3 rash.[61]

Capivasertib plus fulvestrant has also shown antitumor activity in heavily pretreated patients with PTEN-mutated ER+ metastatic breast cancer, particularly in patients with prior progression on fulvestrant.[61] Five to ten percent of ER+ metastatic breast cancer tumors harbor somatic PTEN mutations and loss of function of this tumor-suppressor gene defines a highly aggressive, treatment-refractory disease.[29] In this study, capivasertib was deemed tolerable and clinically active: the 24-week clinical benefit rate was 42% and ORR was 21% in the 19 fulvestrant pre-treated patients.

Ipatasertib (GDC-0068), is another potent and selective ATP-competitive pan-AKT kinase inhibitor where impressive durable antitumor response in combination with fulvestrant has been reported in heavily pre-treated patients with *AKT1 E17K* mutant metastatic breast cancer.[60,66] Ipatasertib is currently being investigated in a monotherapy treatment arm as part of NCI MATCH.[67]

Combination Strategies

There is strong preclinical rationale for AKT inhibitor combination strategies in multiple settings, including acquired resistance to other anti-cancer agents, adaptive *de novo* resistance due to relief of negative feedback, and both chemo- and radio-resistance. AKT activation is implicated as mechanisms of resistance in all of these scenarios. Thus, AKT inhibitors are currently being tested in combination with a range of chemotherapeutic and targeted agents.

Chemotherapy Combinations

Activation of AKT has been linked to resistance in both chemotherapy and radiotherapy. DNA-PK is one of the apical kinases involved in DNA double strand break repair and is essential for classical non-homologous end-joining, the predominant repair pathway of DSBs in human cells.[68] AKT is activated in a DNA-PK–dependent manner following the generation of DNA DSBs, and promotes survival through anti-apoptotic mechanisms.[69,70] AKT inhibition has also been shown, in pre-clinical models, to sensitize cells to a number of chemotherapeutic agents.[71–73]

Until recently, the most encouraging data in combination chemotherapy data was in metastatic TNBC, based upon randomized phase II trials that demonstrated an improvement in clinical outcomes (progression-free survival (PFS) and overall survival (OS)) with paclitaxel in combination with AKT inhibition versus paclitaxel alone.[39,74] A recently reported randomized phase III trial in the first-line setting for TNBC has however dampened enthusiasm for this combination strategy. Presented at the 2020 San Antonio Breast Cancer Symposium, the analysis of IPATunity130 Cohort A assessed the combination of ipatasertib with paclitaxel chemotherapy versus paclitaxel chemotherapy alone, in patients with metastatic TNBC, and showed no difference in both PFS and OS.[75] This trial selected TNBC patients with PIK3CA/AKT1 or PTEN pathway alterations, and given the recently updated survival benefit shown in the in the LOTUS phase II trial in TNBC with these alterations,[41] the lack of clinical benefit in this biomarker-selected group of TNBC patients is disappointing.

Prostate cancer is another notable area of development in the AKT field. In the PROCAID trial, capivasertib (AZD5363) was combined with docetaxel and prednisolone in a Phase I trial for patients with metastatic castration-resistant prostate cancer (CRPC): the combination was well tolerated and a recommended Phase II dose was determined for this combination.[76] In the recently reported Phase II trial, the addition of capivasertib to chemotherapy did not extend PFS in metastatic CRPC, irrespective of PI3K/AKT/PTEN pathway activation status.[77] However, a significant improvement in OS, a secondary endpoint, was observed (median OS was 31.15 months in the capivasertib group vs 20.27 months in the placebo group (HR = 0.54, 95% CI = 0.34–0.88, P = 0.01), which will need to be validated prospectively in future studies.

Targeted Therapy Combinations

Increasingly, AKT inhibitor combination strategies have involved molecularly targeted agents. These data are summarized below and in Table 1.[78]

Table 1 Trials Including Combination Strategies with AKT Inhibitors

Reported AKT Combination Trials												
Phase	**NCT**	**Population**	**Biomarker Required**	**AKT Inhibitor**	**Combination Agent**	**Comparator Agent (s)**	**N**	**DCR/ CBR**	**ORR**	**PFS**	**OS**	**Ref**
Combinations with Chemotherapy												
3	NCT01097018	CRC	None	Perifosine	Capecitabine	Capecitabine + Placebo	468	NR	NR*	6.4 v 6.8 m	[114]*	
1b	NCT 01653912	PPROC	None	Afuresertib	Carbo + Paclitaxel	None	59	NR	32%	7.1m	[115]	
		PROC										
1b	NCT02476955	Solid Tumors	None	Miransertib (ARQ092)	Carboplatin + Paclitaxel	None	13	NR	31%	NR	[116]	
				Miransertib (ARQ092)	Paclitaxel		NR	NR	NR	NR	NR	
		Endometrial Cancer	AKT1, PIK3CA, or PIK3R1 mutations in endometrial Ca	Miransertib (ARQ092)	Anastrozole		NR	NR	NR	NR	NR	
Targeted Combinations												
1	NCT01476137	Solid Tumors + Myeloma	None	Afuresertib	Trametinib	None	20	25%	5%	NR	NR	[117]
1	NCT02338622	Solid Tumors	Germline BRCA1/2; BRCA WT with somatic DDR or AKT alterations	Capivasertib (AZD5363)	Olaparib	None	56	44.6%	25% RECIST 34 Tumor Response**	NR	NR	[100]
1/2	NCT02208375	TNBC, Ovarian, primary peritoneal, fallopian tube, or Endometrial	None	Capivasertib (AZD5363)	Olaparib	None	30	NR	24% overall	NR	NR	[118]
									50% endometrial			
1	NCT02525068	mCRPC	None	Capivasertib (AZD5363)	Enzalutamide	None	15	NR	20%	NR	NR	[105]
1	NCT04087174	mCRPC	None	Capivasertib (AZD5363)	Abiraterone	None	15	NR	20%**	NR	NR	[106]

1	NCT01281163	Solid Tumors	None; HER2 + BC expansion cohort	MK-2206	Lapatinib	None	28	14%	0%	NR	NR	[91]
1	NCT01021748	Solid Tumors	None; KRAS NSCLC expansion cohort	MK-2206	Selumetinib (AZD6244)	None	51	NR	14%	NR	NR	[92]
2	NCT01333475	CRC	KRAS mutant versus KRAS WT	MK-2206	Selumetinib (AZD6244)	None	21	8%	0%	NR	NR	[93]
2	NCT01658943	Pancreatic CA	None	MK-2206	Selumetinib (AZD6244)	mFOLFOX	137	NR	3% v 22%	1.9 v 2.0m	3.9 v 6.7m	[94]
2	NCT01964924	TNBC	None	GSK2141795	Trametinib	None	16	NR	6%	NR	NR	[86]
1	NCT01138085	TNBC or BRAF WT Melanoma	None	Uprosertib (GSK 2141795)	Trametinib	None	126	NR	4.8%	TNBC= 56d MM= 114d	NR	[81]
1	NCT01935973	Endometrial Cancer	None	Uprosertib (GSK 2141795)	Trametinib	None	26	NR	8.3%	3.4m	NR	[80]
2	NCT01941927	BRAF WT Melanoma	NRAS Mutant versus NRAS WT	Uprosertib (GSK 2141795)	Trametinib	None	20	65%	0%	2.75	NR	[82]
2	NCT01979523	Uveal Melanoma	None	Uprosertib (GSK 2141795)	Trametinib	Trametinib Alone	40	NR	5% v 6%	15.6 v 15.7 weeks	NR	[83]
1/2	NCT01902173	Solid Tumors	BRAF-V600E/K mutant	Uprosertib (GSK 2141795)	Trametinib + Dabrafenib	None	11	NR	50%	NR	NR	[85]
				Uprosertib (GSK 2141795)	Dabrafenib		9	NR	38%	NR	NR	
2	NCT01958112	Cervical CA	None	Uprosertib (GSK2141795)	Trametinib	None	14	57%	8%	NR	NR	[87]

(*Continued*)

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Table 1 (Continued).

Reported AKT Combination Trials												
Phase	**NCT**	**Population**	**Biomarker Required**	**AKT Inhibitor**	**Combination Agent**	**Comparator Agent (s)**	**N**	**DCR/ CBR**	**ORR**	**PFS**	**OS**	**Ref**
1	NCT01147211	NSCLC	EGFR mutant	MK-2206	Gefitinib	None	14	NR	0%	NR	NR	[90]
1b	NCT01562275	Solid Tumors	None; Expansion in PTEN deficient, TNBC, or endometrial CA	Ipatasertib (GDC-0068)	Cobimetinib (GDC-0973)	None	66	47%	5%	NR	NR	[58]
2	NCT01294306	NSCLC EGFR mutant	Stratified by EGFR mutant status	MK2206	Erlotinib	None	45	40%	9%	4.4m	NR	[119]
		EGFR WT					35	47%	4%	4.6m		
Combination with Hormones												
2	NCT01251861	High Risk Prostate Cancer	None	MK2206	Bicalutamide	Bicalutamide	108	NR	NR	NR	NR	[104]
1b	NCT03959891	HR+/HER2 – MBC	None	Ipatasertib	Fulvestrant + Palbociclib	None	12	NR	17%	NR	NR	[96]
1	NCT01344031	Metastatic Breast Cancer	None	MK2206	Anastrozole with or without fulvestrant	None	31	NR	7.7%	NR	NR	[42]
2	NCT01992952	ER+ MBC after AI	None	Capivasertib	Fulvestrant	Fulvestrant Alone	140	NR	29% v 8%	10.3 v 4.8m	23.7 v 20.3m	[44]
3	NCT03072238	mCRPC	Stratified by PTEN loss by IHC ≥50% tumor cells	Ipatasertib	Abiraterone	Placebo + Abiraterone	1101	NR	NR	PTEN Loss: 19.1 v 14.2 m	NE	[108]
									ITT: 61 v 44%	ITT: 19.2 v 16.6 m		
Ongoing AKT Inhibitor Trials Without Reported Results												
Phase	NCT	Selection Criteria		AKT Drug	Combination	Comparator						
1	NCT01783171	Pancreatic Cancer	None	MK2206	Dinaciclib (SCH727965)	None						

1	NCT01705340	HER2+ Breast, GE, or gastric	HER2 +	MK2206	Trastuzumab + Lapatinib	None				
1	NCT04253561	HER2 Positive BC	PI3K mutant	Ipatasertib	Pertuzumab + Trastuzumab	None				[97]
2	NCT04374630	Platinum Resistant Ovarian Cancer	None	Afuresertib	Paclitaxel	Paclitaxel alone				
2	NCT04467801	Metastatic/Advanced NSCLC	None	Ipatasertib	Docetaxel	None				

Notes: *Not reported but noted to be not improved; **Partial or complete response or GCIG or PCWG2 responses.
Abbreviations: CRC, colorectal cancer; Mut, mutant; NR, not reported; NE, not yet evaluable; PPROC, primary platinum refratory ovarian cancer; PROC, platinum resistant ovarian cancer; WT, wild type.

Uprosertib (GSK2141795)

Alterations in the PI3K and RAS pathways have been implicated in tumorigenesis of endometrial cancer and are associated with poor treatment outcomes.[79] Treatment with single-agent AKT inhibitors has, however, led to modest results. In a phase I/II study, the ATP-competitive AKT inhibitor uprosertib (GSK2141795) and MEK1/2 inhibitor trametinib were assessed in refractory or persistent endometrial cancer. The combination was poorly tolerated and clinical benefit was limited with only one response observed in 12 (8.3%) patients. The median PFS was only 3.4 months and the Phase II study was not initiated due to toxicity and a lack of efficacy.[80] Another phase I trial in TNBC and BRAF-WT melanoma investigated the combination of uprosertib and trametinib.[81] This was poorly tolerated, with over half of all patients experiencing DLTs and preventing dose escalation to dose levels predicted to have clinical activity. The ORR amongst 126 treated patients was <5%. In a phase II study of the same combination in BRAF WT melanoma including 24 NRAS WT and 24 *NRAS* mutant melanomas, 65% of patients achieved stable disease as their best response, however no objective responses were observed. Median PFS was only 2.75 months with no difference by *NRAS* mutation status.[82] The combination was also found to add no PFS or ORR benefit in a separate Phase 2 trial in uveal melanoma when compared to trametinib alone.[83]

In BRAF-V600E/K mutant advanced solid tumors including melanoma, aberrant PI3K/AKT signaling may contribute to resistance of MAPK pathway blockade.[84] The Phase I/II SWOG S1221 study was conducted to combine uprosertib with dabrafenib with or without trametinib. Both the doublet and triplet combinations were generally well tolerated. In the doublet cohort (n = 8), 2 of 2 treatment-naive patients had PRs, while only 1 of 6 BRAF refractory melanoma patients achieved an objective response. In the triplet cohort, 3 of 6 treatment-naïve patients had PRs. Diarrhea and rash were common dose-limiting toxicities, with 59% of patients experiencing grade 3 toxicities.[85]

In a two-part single-arm study of metastatic TNBC, trametinib was administered alone in part 1 and in combination with uprosertib upon progression in part 2. In the combination arm, only one of 16 patients experienced an unconfirmed PR and GI toxicities were common.[86] Given that *PIK3CA* and *KRAS* mutations are common in both adenocarcinoma and squamous cell carcinoma of the

cervix, the combination of uprosertib and trametinib has been evaluated in a phase II trial, however, due to manufacturer discontinuation of uprosertib, the trial was halted early. At the time of termination, 14 patients had received study drug with one partial response of 12 evaluable patients.[87]

MK-2206

The PI3K/AKT signaling pathway is important for epidermal growth factor receptor (EGFR) signaling and may be a mechanism of resistance to EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC), which is supported by improved preclinical activity with combination blockade.[88,89] To this end, MK-2206 was combined with gefitinib in patients with metastatic NSCLC who had progressed following at least 3 months treatment of EGFR TKI. Fourteen patients were treated, two patients had minor tumor regressions, but no objective responses were observed, and hematologic toxicities were dose limiting.[90] In a phase I study, MK-2206 was combined with the anti-HER2 agent, lapatinib, in patients with advanced solid tumors. Two of 23 patients in the dose escalation phase maintained stable disease for greater than 4 months, as did 2 of 5 patients in the cohort expansion phase of HER2 positive breast cancers. The overlapping toxicities of rash and diarrhea were typically grade 1–2 and were managed effectively using supportive measures.[91] In an effort to undertake dual vertical blockade of the pathway, MK-2206 has also been combined with the MEK inhibitor, selumetinib, in advanced *KRAS* mutant cancers. Four durable responses were observed in 3 of 13 (23%) in NSCLC and 1 of 2 patients with ovarian cancers. Common dose limiting toxicities included stomatitis, diarrhea, fatigue, and retinal pigment epithelium detachment.[92] This combination was subsequently assessed in advanced colorectal cancer patients and stratified by *KRAS* mutations, however no objective responses were observed among twenty-one enrolled patients and the pre-specified target response criteria of 70% inhibition of phosphorylated ERK and AKT levels in paired tumor biopsies was not met.[93]

In attempts to target KRAS through downstream inhibition of MEK and PI3K/AKT pathways in pancreatic cancer, 137 patients with metastatic pancreatic cancer who progressed following gemcitabine-based chemotherapy were randomized to MK-2206 with selumetinib or mFOLFOX. Only two responses out of 39 patients were observed in the experimental doublet-targeted therapy arm and overall survival was not improved compared to mFOLFOX (3.9 v 6.7, HR 1.38, p = 0.15).[94]

Ipatasertib (GDC-0068)

Preclinical studies have indicated that CDK4/6 resistance is driven through AKT1 activation, providing rationale for the combination of an AKT inhibitor and CDK4/6 inhibitors.[95] The ongoing phase 1b TAKTIC trial combined the AKT inhibitor ipatasertib (GDC-0068) with fulvestrant, or used a triplet combination of fulvestrant with ipatasertib and palbociclib for the treatment of HR+ HER2 negative metastatic breast cancer, following at least 1 prior therapy and up to 2 lines of chemotherapy. Preliminary results of the triplet combination have shown two partial responses amongst 12 patients, and the combination was well tolerated with no dose limiting toxicities at reported dose levels.[96]

A phase Ib trial of cobimetinib and ipatasertib was however poorly tolerated and all 66 patients who received study drug reported an adverse event, with 53% experiencing drug-related AE of grade 3 or worse severity, though none were dose-limiting toxicities. Although biomarker analyses indicated blockade of combined RAS/MEK/ERK and pI3K/AKT/mTOR pathways in paired tumor biopsies, objective responses were only observed in two patients with endometrial cancer and one with ovarian cancer.[58] A phase I trial has been registered to begin enrollment in HER2 positive metastatic breast cancers with PI3K pathway mutations utilizing the triplet combination of ipatasertib with anti-HER2 agents pertuzumab and trastuzumab (NCT04253561).[97]

Capivasertib (AZD5363)

Preclinical studies have demonstrated synergy between PARP and PI3K/AKT pathway inhibitors in BRCA1 and BRCA2 (BRCA1/2)–deficient and BRCA1/2-proficient tumors.[98,99] Consequently, the combination is being explored in clinical trials. In a phase I trial, PARP inhibitor olaparib in combination with capivasertib was well tolerated and antitumor activity was observed as twenty-five (44.6%) of 56 evaluable patients achieved clinical benefit (RECIST complete response/partial response or stable disease ≥4 months), including patients with tumors harboring germline BRCA1/2 mutations and BRCA1/2 wild-type cancers with or without DDR and PI3K–AKT pathway alterations.[100] Five (71.4%) of 7 patients with germline BRCA1/2-mutant breast cancers achieved clinical benefit, and antitumor responses were also observed in patients

who had previously developed disease progression on PARP and PI3K pathway inhibitors.[100] Although based on small numbers, this study supports the combination of capivasertib with olaparib as a rational strategy to potentially improve patient benefit beyond that of single-agent olaparib.

Endocrine Therapy Combinations

Hyperactivation of the PI3K-AKT pathway is associated with endocrine resistance in estrogen receptor-positive breast cancer.[101,102] In a Phase II (NCT01776008) trial in stage II or III ER+ and HER2-negative breast cancer with *PI3KCA* mutations, MK-2206 was combined anastrozole, an aromatase inhibitor, in the neoadjuvant setting. The primary endpoint was the pathologic complete response rate at the time of surgery. A cycle 1 day 17 biopsy was performed and if Ki67 was greater than 10%, treatment would be discontinued. Fifty-one patients were preregistered and 16 of 22 patients with *PIK3CA* mutant tumors received study treatments. Two patients discontinued study due to high Ki67 and 1 due to toxicity. Of 13 patients who completed neoadjuvant therapy, no pathologic complete responses were observed.[103]

A Phase 1 study of MK-2206 combined with hormonal therapies evaluated 31 postmenopausal women with ER positive MBC. Grade 3 rash was the main dose-limiting toxicity, which was ameliorated with prophylactic prednisone. The overall response rate was however only 7.7% and did not correlate with *PIK3CA* mutation status. In the combination with anastrozole, two partial responses were observed in 13 patients, with no partial responses noted in the combination with fulvestrant, or with anastrozole (n = 6) and fulvestrant (n = 6).[42] The FAKTION trial evaluated the addition of capivasertib to fulvestrant in a double-blind placebo-controlled phase 2 trial. Following disease progression on an aromatase inhibitor, patients with HER2-negative metastatic or locally advanced breast cancer were enrolled to receive 400mg of capivasertib or matching placebo with IM fulvestrant. A total of 140 patients were enrolled. PFS was improved to 10.3 months in the capivasertib group versus 4.8 months in the placebo group, with HR of 0.58 (95% CI 0.39–0.84, p = 0.0018). For the combination therapy, PFS was improved in non-PI3K /PTEN pathway mutated cancers (HR = 0.56, p = 0.035) and non-significantly improved in PI3K/PTEN pathway mutated tumors (HR = 0.59, p = 0.064). Compared to placebo, the most common adverse events in combination were hypertension, diarrhea, and infection.[44]

In castration-resistant prostate cancer (CRPC), activation of the PI3K/AKT/mTOR pathway through loss of phosphatase and tensin homolog (PTEN) occurs in approximately 50% of patients with metastatic CRPC; the combination of androgen deprivation with AKT inhibition is thus postulated to improve PSA responses. A phase II trial of bicalutamide combined with MK-2206 versus bicalutamide alone was conducted in men with high risk localized prostate cancer after local therapy with PSA recurrence and fast doubling time with a primary endpoint of PSA ≤0.2. A non-statistically significant improvement in PSA response of 35.6% (16/45) was noted in the combination arm versus 20.4% (10/49) in the bicalutamide alone arm (p = 0.08).[104] In patients with metastatic CRPC progressing on abiraterone and/or enzalutamide, a phase I trial investigated escalating doses of capivasertib with continuous enzalutamide dosing.[105] The combination was safe and well tolerated and antitumor activity was observed in patients with PTEN loss or activating mutations in AKT, low or absent AR-V7 expression, as well as those with an increase in phosphorylated extracellular signal-regulated kinase (pERK) in post-exposure samples.[105] Similarly, interim results of a phase 1 study in metastatic CRPC combining abiraterone and capivasertib in 15 patients reported acceptable safety and tolerability (rash, diarrhea, and hyperglycemia as the most common adverse events). Five patients had reduced PSA levels (>20%) on treatment, with 3 patients showing sustained falls in PSA over 12 weeks.[106]

Consistent with encouraging phase I data, a randomized Phase II trial demonstrated that ipatasertib in combination with abiraterone, results in prolonged radiographic progression-free survival (rPFS) over placebo with abiraterone.[107] The effect on rPFS was even greater in patients with PTEN-loss in tumors compared to those with intact PTEN. As a result, the IPATential150 randomized, Phase III trial of abiraterone with ipatasertib 400 mg PO QD vs abiraterone with placebo was developed and recently reported data are encouraging.[108] Radiological PFS was improved in the ipatasertib plus abiraterone group over the placebo plus abiraterone group (median rPFS 18.5 vs 16.5 months, respectively), with a stratified hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.61–0.98, p = 0.0335, statistical significance set at α=0.05). Post-hoc analysis of rPFS in the next-generation sequencing defined PTEN-loss population was also significant with a median rPFS 19.1 vs 14.2 months, respectively (HR 0.65; 95% CI 0.45–0.95, p = 0.0206),

while secondary endpoints of confirmed ORR, PSA response, and time to PSA progression all favored the ipatasertib arm. While overall survival data are not yet mature, these data are encouraging and may allow us to better learn how to identify and define the PTEN-loss population.

Toxicity Profile of AKT Inhibitors

There are a number of well-defined toxicities related to the pharmacological inhibition of the AKT/PI3K pathway,[109] and safety and tolerability issues have likely hampered the development of some AKT inhibitors (eg, MK2206). The toxicity spectrum of AKT inhibitors becomes increasingly important in the context of developing combination strategies and in novel clinical trial design. Dermatological toxicities are typically observed with all AKT inhibitors; for example, in the phase I trial of MK-2206 monotherapy, DLTs were skin rash and stomatitis, and drug-related skin AEs were frequent; these included rash (51.5%) and pruritus (24.2%).[56] Skin toxicities were also frequent in Phase I–II trials of capivasertib or ipatasertib, although the overall incidence of grade ≥3 adverse events, comparably, was lower with these compounds.[7,110,111] Diarrhea is another well-known and frequent toxicity, and a DLT in early dose-finding trials,[50,56] even though it was for the majority, mild or moderate (8–23% incidence of grade 3 or higher). Diarrhea tends to occur early in onset of treatment, but is reversible following treatment discontinuation and optimum management with anti-diarrheal agents, such as loperamide. Hyperglycemia is a well-defined class toxicity of AKT/PI3K inhibitors,[42,50,61] as insulin-mediated glucose homeostasis, appears to largely depend on PI3K signaling via GSK3β and FOXO,[109] though the incidence of hyperglycemia of any grade in clinical trials of AKT inhibitors has varied, for example from 21.2% in the monotherapy MK2206 phase I trial,[56] to 92% with MK-2206 and anastrozole trial,[42] and as low as 4% with ipatasertib and paclitaxel.[41] Phase I trials of capivasertib and ipatasertib have also shown considerable grade 3 or higher incidence of hyperglycemia, albeit with no documented reports of hyperosmolar coma or ketoacidosis,[50,65] though increasingly, it is clear that improved patient selection and aggressive patient optimization, including dietary intervention, glucose lowering medications, and treatment interruption with or without dose modifications can help with this class-specific toxicity.

To date, the close homology between the three AKT isoforms has hampered the development of isoform-specific AKT inhibitors, though perhaps the development of isoform-specific AKT inhibitors could avoid some of the toxicities that pan-AKT inhibitors cause and could be a strategy which may improve their side-effect profile as a class.

Future Directions

Moving forward, a more detailed understanding of the biology of AKT, including perhaps the development of isoform-specific AKT inhibitors, and the continued use of innovative clinical trial design will be important. Due to the rarity of some of the alterations in AKT, recently adapted novel trial designs, such as the basket trial of AKT inhibitor capivasertib in *AKT1* E17K mutant solid tumors, and adaptive platform trials (such as the Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study, NCT04589845) will likely be important. Novel AKT inhibitors are also under investigation: for example borussertib, a first-in-class covalent-allosteric AKT inhibitor has recently been developed and is showing anti-proliferative activity in cell lines and xenograft models when combined with the MEK inhibitor trametinib.[112] Interestingly, a nanoparticle-encapsulated version of capivasertib has also been developed and tested in radio-resistant models of head and neck squamous cell carcinoma which may have the potential to achieve better treatment outcomes than the free drug combination.[113]

Conclusions

AKT is a key factor in cell survival and growth, with dysregulation of AKT implicated in a number of solid tumors. AKT remains an attractive target for cancer therapy as it is a central node along a key oncogenic pathway, where it diverges and integrates with signals from other important pathways. There is a veritable plethora of studies that support the role of AKT as a well-validated target for drug development, and while the translation of AKT inhibition into therapeutic benefit has been complex, recent clinical successes using combination strategies, particularly in breast cancer, while modest, are driving enthusiasm in the field. The multiple layers of AKT pathway regulation clearly impair our ability to more accurately predict efficacy to AKT inhibitors and only by delving more into the biology of the complex web of AKT pathway interactions will progress be made.

Looking to the future, the continued incorporation of tumor biopsies and analyses of ctDNA as part of biomarker-

driven clinical trials will be critical in uncovering potential biomarkers of response and resistance to AKT inhibitors. To address the issues of suboptimal drug exposures due to toxicities, the development of such predictive biomarkers to optimally select patients, together with proof of target modulation are likely to be vital in the development of AKT inhibitors. Overcoming these challenges will enable genuine progress to be made in the development of AKT inhibitors for patients with cancer on a personalized basis, to improve outcomes and transform patient care.

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